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 s l1 and MAP kinase inhibitor
L2          71 L1 AND MAP KINASE INHIBITOR

=> s l2 and ErbB2
L3           0 L2 AND ERBB2

=> s l2 and pd<20021121
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L4          19 L2 AND PD<20021121

=> d l4 1-19 cbib abs

L4   ANSWER 1 OF 19     MEDLINE on STN
2002460303.    PubMed ID: 12218287.   A simple technique for high-throughput
     screening of drugs that modulate normal and psoriasis-like
     differentiation in cultured human keratinocytes. Pol Arno; Bergers Mieke;
     van Ruissen Fred; Pfundt Rolph; Schalkwijk Joost. (Department of
     Dermatology, University Hospital, Nijmegen, The Netherlands..
     a.pol@derma.azn.nl) . Skin pharmacology and applied skin physiology,
     (2002 Jul-Aug) Vol. 15, No. 4, pp. 252-61.  Journal code: 9807277.
     ISSN: 1422-2868. Pub. country: Switzerland. Language: English.
AB   Established treatments for psoriasis act ei-ther on
     hyperproliferation, inflammation, aberrant epidermal differentiation or a
     combination of these aspects of the disease.  Potential new drugs for
     treatment of psoriasis or other disorders with abnormalities in
     epidermal differentiation can be identified by high-throughput screening
     of large compound libraries using surrogate markers for the disease.  Here
     we describe a screening model to detect pharmacologically active drugs in
     two keratinocyte-based, 96-well culture models that use expression of
     cytokeratin 10 (CK10) and skin-derived antileucoprotease (SKALP)/elafin as
     markers for normal and psoriatic differentiation, respectively, and allow
     multiple parameters to be determined from a single well.  In this model we
     tested a number of compounds in a pharmacological range from 10(-7) to
     10(-5) M, including known antipsoriatic drugs, and experimental drugs that
     are potentially useful in the treatment of psoriasis.
     All-trans-retinoic acid, dithranol and the p38 mitogen-activated protein (
     MAP) kinase inhibitor SB220025 displayed a
     strong inhibitory effect on SKALP expression while cyclosporin A,
     dexamethasone, the vitamin D(3) derivative calcipotriol and the p38
     MAP kinase inhibitor SB203580 showed only
     moderate inhibition.  Methotrexate and dimethylfumarate did not affect the
     expression of SKALP.  With respect to CK10 expression, all-trans-retinoic
     acid, calcipotriol, SB203580 and SB220025 exhibited strong inhibition
     while dithranol showed only moderate suppression of this normal
     differentiation marker.  Expression levels of CK10 were not significantly
     affected by dexamethasone, methotrexate, cyclosporin A or
     dimethylfumarate.  This model system parallels most, but not all, findings
     on the in vitro effect of known antipsoriatic drugs on keratinocytes.  In
     addition, the model identifies p38 MAP kinase
     inhibitors as potent suppressors of differentiation-associated
     gene expression.  Although further delineation and validation of this
     model is required, we conclude that the system is amenable to down-scaling
     and application as a high-throughput screen for differentiation-modifying
     compounds.
     Copyright 2002 S. Karger AG, Basel

L4   ANSWER 2 OF 19     MEDLINE on STN
2000294600.    PubMed ID: 10836611.   TNF-alpha and serum induce SKALP/elafin
     gene expression in human keratinocytes by a p38 MAP kinase-dependent
     pathway. Pfundt R; Wingens M; Bergers M; Zweers M; Frenken M; Schalkwijk
     J. (Department of Dermatology, University Hospital Nijmegen, The
     Netherlands. ) Archives of dermatological research, (2000 Apr)
     Vol. 292, No. 4, pp. 180-7.  Journal code: 8000462. ISSN: 0340-3696. Pub.
     country: GERMANY: Germany, Federal Republic of. Language: English.
```

AB Keratinocytes of inflamed epidermis (**psoriasis**, wound healing) are hyperproliferative and display an abnormal differentiation programme. This regenerative differentiation pathway is characterized by the induction of genes that are not expressed by keratinocytes in normal skin, such as the cytokeratins CK6, CK16, CK17, and the proteinase inhibitor SKALP/elafin. In the study reported here we investigated the induction and regulation of SKALP expression as a marker for regenerative differentiation in epidermal keratinocytes. Various cytokines and growth factors known to be present in psoriatic epidermis were examined for their ability to induce SKALP gene expression in cultured human keratinocytes. Tumour necrosis factor-alpha (TNF-alpha) and serum were found to be potent inducers of SKALP expression at both the mRNA and the protein levels. SB202190 or SB203580, two specific p38 **MAP kinase inhibitors** almost completely blocked the induction of SKALP expression by TNF-alpha and serum. These results suggest that in keratinocytes, p38 activity is crucial for the induction of SKALP gene expression. These findings could be relevant for the elucidation of the mechanisms involved in normal and disturbed epidermal differentiation.

L4 ANSWER 3 OF 19 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2002344533 EMBASE A simple technique for high-throughput screening of drugs that modulate normal and **psoriasis**-like differentiation in cultured human keratinocytes. Pol A.; Bergers M.; Van Ruissen F.; Pfundt R.; Schalkwijk J.. A. Pol, Department of Dermatology, University Hospital, PO Box 9101, NL-6500 HB Nijmegen, Netherlands. a.pol@derma.azn.nl. Skin Pharmacology and Applied Skin Physiology Vol. 15, No. 4, pp. 252-261 **2002**.

Refs: 25.

ISSN: 1422-2868. CODEN: SPAPFF

Pub. Country: Switzerland. Language: English. Summary Language: English.

Entered STN: 20021010. Last Updated on STN: 20021010

AB Established treatments for **psoriasis** act either on hyperproliferation, inflammation, aberrant epidermal differentiation or a combination of these aspects of the disease. Potential new drugs for treatment of **psoriasis** or other disorders with abnormalities in epidermal differentiation can be identified by high-throughput screening of large compound libraries using surrogate markers for the disease. Here we describe a screening model to detect pharmacologically active drugs in two keratinocyte-based, 96-well culture models that use expression of cytokeratin 10 (CK10) and skin-derived antileucoprotease (SKALP)/elafin as markers for normal and psoriatic differentiation, respectively, and allow multiple parameters to be determined from a single well. In this model we tested a number of compounds in a pharmacological range from 10-(7) to 10-(5) M, including known antipsoriatic drugs, and experimental drugs that are potentially useful in the treatment of **psoriasis**. All-trans-retinoic acid, dithranol and the p38 mitogen-activated protein (**MAP**) **kinase inhibitor** SB220025 displayed a strong inhibitory effect on SKALP expression while cyclosporin A, dexamethasone, the vitamin D(3) derivative calcipotriol and the p38 **MAP kinase inhibitor** SB203580 showed only moderate inhibition. Methotrexate and dimethylfumarate did not affect the expression of SKALP. With respect to CK10 expression, all-trans-retinoic acid, calcipotriol, SB203580 and SB220025 exhibited strong inhibition while dithranol showed only moderate suppression of this normal differentiation marker. Expression levels of CK10 were not significantly affected by dexamethasone, methotrexate, cyclosporin A or dimethylfumarate. This model system parallels most, but not all, findings on the in vitro effect of known antipsoriatic drugs on keratinocytes. In addition, the model identifies p38 **MAP kinase inhibitors** as potent suppressors of differentiation-associated gene expression. Although further delineation and validation of this model is required, we conclude that the system is amenable to down-scaling and application as a high-throughput screen for differentiation-modifying

compounds. Copyright .COPYRGT. 2002 S. Karger AG, Basel.

L4 ANSWER 4 OF 19 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2000156765 EMBASE TNF-α and serum induce SKALP/elafin gene expression in human keratinocytes by a p38 MAP kinase-dependent pathway. Pfundt R.; Wingens M.; Bergers M.; Zweers M.; Frenken M.; Schalkwijk J.. J. Schalkwijk, Department of Dermatology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands. J.Schalkwijk@derma.azn.nl. Archives of Dermatological Research Vol. 292, No. 4, pp. 180-187 **2000**.
Refs: 55.
ISSN: 0340-3696. CODEN: ADMFAU
Pub. Country: Germany. Language: English. Summary Language: English.
Entered STN: 20000518. Last Updated on STN: 20000518

AB Keratinocytes of inflamed epidermis (**psoriasis**, wound healing) are hyperproliferative and display an abnormal differentiation programme. This regenerative differentiation pathway is characterized by the induction of genes that are not expressed by keratinocytes in normal skin, such as the cytokeratins CK6, CK16, CK17, and the proteinase inhibitor SKALP/ elafin. In the study reported here we investigated the induction and regulation of SKALP expression as a marker for regenerative differentiation in epidermal keratinocytes. Various cytokines and growth factors known to be present in psoriatic epidermis were examined for their ability to induce SKALP gene expression in cultured human keratinocytes. Tumour necrosis factor-alpha (TNF-α) and serum were found to be potent inducers of SKALP expression at both the mRNA and the protein levels. SB202190 or SB203580, two specific p38 **MAP kinase inhibitors** almost completely blocked the induction of SKALP expression by TNF-α and serum. These results suggest that in keratinocytes, p38 activity is crucial for the induction of SKALP gene expression. These findings could be relevant for the elucidation of the mechanisms involved in normal and disturbed epidermal differentiation.

L4 ANSWER 5 OF 19 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2002:600901 Document No.: PREV200200600901. A simple technique for high-throughput screening of drugs that modulate normal and **psoriasis**-like differentiation in cultured human keratinocytes. Pol, Arno [Reprint author]; Bergers, Mieke; van Ruissen, Fred; Pfundt, Rolph; Schalkwijk, Joost. Department of Dermatology, University Hospital, NL-6500 HB, PO Box 9101, Nijmegen, Netherlands. a.pol@derma.azn.nl. Skin Pharmacology and Applied Skin Physiology, (**July-August, 2002**) Vol. 15, No. 4, pp. 252-261. print.
ISSN: 1422-2868. Language: English.

AB Established treatments for **psoriasis** act either on hyperproliferation, inflammation, aberrant epidermal differentiation or a combination of these aspects of the disease. Potential new drugs for treatment of **psoriasis** or other disorders with abnormalities in epidermal differentiation can be identified by high-throughput screening of large compound libraries using surrogate markers for the disease. Here we describe a screening model to detect pharmacologically active drugs in two keratinocyte-based, 96-well culture models that use expression of cytokeratin 10 (CK10) and skin-derived antileucoprotease (SKALP)/elafin as markers for normal and psoriatic differentiation, respectively, and allow multiple parameters to be determined from a single well. In this model we tested a number of compounds in a pharmacological range from 10-7 to 10-5 M, including known antipsoriatic drugs, and experimental drugs that are potentially useful in the treatment of **psoriasis**. All-trans-retinoic acid, dithranol and the p38 mitogen-activated protein (**MAP**) **kinase inhibitor** SB220025 displayed a strong inhibitory effect on SKALP expression while cyclosporin A, dexamethasone, the vitamin D3 derivative calcipotriol and the p38 **MAP kinase inhibitor** SB203580 showed only

moderate inhibition. Methotrexate and dimethylfumarate did not affect the expression of SKALP. With respect to CK10 expression, all-trans-retinoic acid, calcipotriol, SB203580 and SB220025 exhibited strong inhibition while dithranol showed only moderate suppression of this normal differentiation marker. Expression levels of CK10 were not significantly affected by dexamethasone, methotrexate, cyclosporin A or dimethylfumarate. This model system parallels most, but not all, findings on the in vitro effect of known antipsoriatic drugs on keratinocytes. In addition, the model identifies p38 **MAP kinase inhibitors** as potent suppressors of differentiation-associated gene expression. Although further delineation and validation of this model is required, we conclude that the system is amenable to down-scaling and application as a high-throughput screen for differentiation-modifying compounds.

L4 ANSWER 6 OF 19 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2001:511112 Document No.: PREV200100511112. In vivo characterization of SB 239063, a novel p38 **MAP kinase inhibitor**.
McAdams, H. A. [Reprint author]; Kou, J. P. [Reprint author]; Truneh, A. [Reprint author]; Davenport, C. M. [Reprint author]. GlaxoSmithKline Pharmaceuticals, 709 Swedeland Rd., King of Prussia, PA, USA. Inflammation Research, (**September, 2001**) Vol. 50, No. Supplement 3, pp. S205. print.
Meeting Info.: 5th World Congress on Inflammation. Edinburgh, Scotland. September 22-26, 2001.
ISSN: 1023-3830. Language: English.

L4 ANSWER 7 OF 19 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2001:493520 Document No.: PREV200100493520. SB239063, a p38 **MAP kinase inhibitor**, inhibits development of psoriatic lesions as effectively as cyclosporin A in C.B-17 SCID mice adoptively transferred with naive T cells from B10.D2 splenocytes. McAdams, H. [Reprint author]; Truneh, A. [Reprint author]; Kou, J. [Reprint author]; Eichman, C. [Reprint author]; Davenport, C. [Reprint author]. Immunology, SmithKline Beecham, King Of Prussia, PA, USA. Journal of Investigative Dermatology, (**August, 2001**) Vol. 117, No. 2, pp. 463. print.
Meeting Info.: 62nd Annual Meeting of the Society for Investigative Dermatology. Washington, DC, USA. May 09-12, 2001.
CODEN: JIDEAE. ISSN: 0022-202X. Language: English.

L4 ANSWER 8 OF 19 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2000:267247 Document No.: PREV200000267247. TNF-alpha and serum induce SKALP/elafin gene expression in human keratinocytes by a p38 MAP kinase-dependent pathway. Pfundt, Rolph; Wingens, Miriam; Bergers, Mieke; Zweers, Manon; Frenken, Marco; Schalkwijk, Joost [Reprint author]. Department of Dermatology, University Hospital Nijmegen, 6500 HB, Nijmegen, Netherlands. Archives of Dermatological Research, (**April, 2000**) Vol. 292, No. 4, pp. 180-187. print.
CODEN: ADREDL. ISSN: 0340-3696. Language: English.
AB Keratinocytes of inflamed epidermis (**psoriasis**, wound healing) are hyperproliferative and display an abnormal differentiation programme. This regenerative differentiation pathway is characterized by the induction of genes that are not expressed by keratinocytes in normal skin, such as the cytokeratins CK6, CK16, CK17, and the proteinase inhibitor SKALP/elafin. In the study reported here we investigated the induction and regulation of SKALP expression as a marker for regenerative differentiation in epidermal keratinocytes. Various cytokines and growth factors known to be present in psoriatic epidermis were examined for their ability to induce SKALP gene expression in cultured human keratinocytes. Tumour necrosis factor-alpha (TNF-alpha) and serum were found to be potent inducers of SKALP expression at both the mRNA and the protein levels. SB202190 or SB203580, two specific p38 **MAP kinase inhibitors** almost completely blocked the induction of SKALP expression by TNF-alpha and serum. These results suggest that in

keratinocytes, p38 activity is crucial for the induction of SKALP gene expression. These findings could be relevant for the elucidation of the mechanisms involved in normal and disturbed epidermal differentiation.

L4 ANSWER 9 OF 19 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2002:802635 The Genuine Article (R) Number: 596QK. A simple technique for high-throughput screening of drugs that modulate normal and **psoriasis**-like differentiation in cultured human keratinocytes. Pol A (Reprint); Bergers M; van Ruissen F; Pfundt R; Schalkwijk J. Univ Nijmegen Hosp, Dept Dermatol, POB 9101, NL-6500 HB Nijmegen, Netherlands (Reprint); Univ Nijmegen Hosp, Dept Dermatol, NL-6500 HB Nijmegen, Netherlands. SKIN PHARMACOLOGY AND APPLIED SKIN PHYSIOLOGY (**JUL-AUG 2002**) Vol. 15, No. 4, pp. 252-261. ISSN: 1422-2868. Publisher: KARGER , ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Established treatments for **psoriasis** act either on hyperproliferation, inflammation, aberrant epidermal differentiation or a combination of these aspects of the disease. Potential new drugs for treatment of **psoriasis** or other disorders with abnormalities in epidermal differentiation can be identified by high-throughput screening of large compound libraries using surrogate markers for the disease. Here we describe a screening model to detect pharmacologically active drugs in two keratinocyte-based, 96-well culture models that use expression of cytokeratin 10 (CK10) and skin-derived antileucoprotease (SKALP)/elafin as markers for normal and psoriatic differentiation, respectively, and allow multiple parameters to be determined from a single well. In this model we tested a number of compounds in a pharmacological range from 10(-7) to 10(-5) M, including known antipsoriatic drugs, and experimental drugs that are potentially useful in the treatment of **psoriasis**. All-trans-retinoic acid, dithranol and the p38 mitogen-activated protein (**MAP**) **kinase inhibitor** SB220025 displayed a strong inhibitory effect on SKALP expression while cyclosporin A, dexamethasone, the vitamin D-3 derivative calcipotriol and the p38 **MAP kinase inhibitor** SB203580 showed only moderate inhibition. Methotrexate and dimethylfumarate did not affect the expression of SKALP. With respect to CK10 expression, all-trans-retinoic acid, calcipotriol, S8203580 and SB220025 exhibited strong inhibition while dithranol showed only moderate suppression of this normal differentiation marker. Expression levels of CK10 were not significantly affected by dexamethasone, methotrexate, cyclosporin A or dimethylfumarate. This model system parallels most, but not all, findings on the in vitro effect of known antipsoriatic drugs on keratinocytes. In addition, the model identifies p38 **MAP kinase inhibitors** as potent suppressors of differentiation-associated gene expression. Although further delineation and validation of this model is required, we conclude that the system is amenable to down-scaling and application as a high-throughput screen for differentiation-modifying compounds. Copyright (C) 2002 S. Karger AG, Basel.

L4 ANSWER 10 OF 19 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2000:374436 The Genuine Article (R) Number: 314KH. TNF-alpha and serum induce SKALP/elafin gene expression in human keratinocytes by a p38 MAP kinase-dependent pathway. Pfundt R; Wingens M; Bergers M; Zweers M; Frenken M; Schalkwijk J (Reprint). Univ Nijmegen Hosp, Dept Dermatol, POB 9101, NL-6500 HB Nijmegen, Netherlands (Reprint); Univ Nijmegen Hosp, Dept Dermatol, NL-6500 HB Nijmegen, Netherlands. ARCHIVES OF DERMATOLOGICAL RESEARCH (**APR 2000**) Vol. 292, No. 4, pp. 180-187. ISSN: 0340-3696. Publisher: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

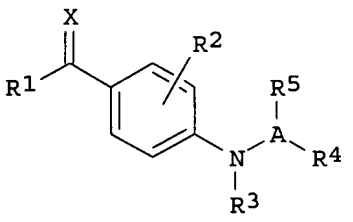
AB Keratinocytes of inflamed epidermis (**psoriasis**, wound healing) are hyperproliferative and display an abnormal differentiation

programme. This regenerative differentiation pathway is characterized by the induction of genes that are not expressed by keratinocytes in normal skin, such as the cytokeratins CK6, CK16, CK17, and the proteinase inhibitor SKALP/elafin. In the study reported here we investigated the induction and regulation of SKALP expression as a marker for regenerative differentiation in epidermal keratinocytes, Various cytokines and growth factors known to be present in psoriatic epidermis were examined for their ability to induce SKALP gene expression in cultured human keratinocytes, Tumour necrosis factor-alpha (TNF-alpha) and serum were found to be potent inducers of SKALP expression at both the mRNA and the protein levels. SB202190 or SB203580, two specific p38 **MAP kinase inhibitors** almost completely blocked the induction of SKALP expression by TNF-alpha. and serum, These results suggest that in keratinocytes, p38 activity is crucial for the induction of SKALP gene expression, These findings could be relevant for the elucidation of the mechanisms involved in normal and disturbed epidermal differentiation.

L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

2002:814087 Document No. 137:325234 Preparation of aminophenyl (hetero)aryl ketones as p38 **MAP kinase inhibitors** for treatment of inflammatory diseases or conditions. Havez, Sophie Elisabeth (Leo Pharma A/S, Den.). PCT Int. Appl. WO 2002083622 A2 **20021024**, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI; SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-DK236 20020410. PRIORITY: US 2001-282494P 20010410.

GI



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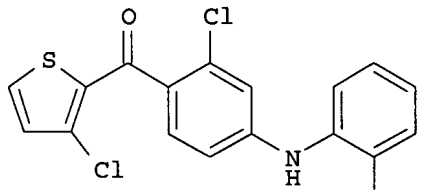


II

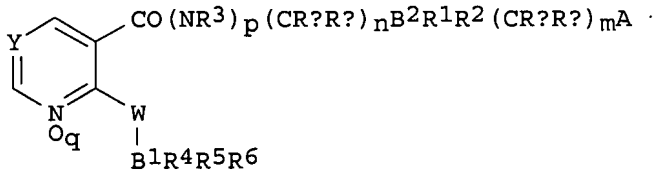
AB Title compds. I [wherein R1 = (un)substituted heteroaryl; X = O, S, N(OH), or NR8; R8 = H or alkyl; R2 = H, halo(alkyl), hydroxy(alkyl), SH, CN, NO2, (cyclo)alkyl, alkenyl, alkynyl, aralkyl, alkylaryl, (ar)alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonylamino, alkylcarboxy, alkylcarbonyl, NR6R7, or CONR6R7; R3 = H, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, CO2H, or aryl; A = (hetero)aryl; R4 = H, halo(alkyl), hydroxy(alkyl), SH, CN, CO2H, NO2, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, heterocycloalkyl, (hetero)aryl, aralkyl, alkylaryl, (ar)alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonylamino, aminocarboaminoalkyl, aminosulfonyl, alkylsulfonylamino, alkylcarboxy, alkoxycarboxy, alkylsulfonyloxy, alkoxysulfonyl, alkylcarbonyl, NR6R7, or CONR6R7; R5 = H, halo(alkyl), hydroxy(alkyl), SH, CN, CO2H, carbamoyl, NH2, NO2, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, heterocycloalkyl, (hetero)aryl, aralkyl, alkylaryl, (ar)alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonylamino, aminocarboaminoalkyl, aminosulfonyl, alkylsulfonylamino, alkylcarboxy, alkoxycarboxy, alkylsulfonyloxy, alkoxysulfonyl, alkylcarbonyl, NR6R7, or CONR6R7; R6 and R7 = independently H, alkyl, aryl, etc.; or pharmaceutically acceptable salts, hydrates, solvates, or esters thereof] were prepared as inhibitors of MAP kinases, in particular the p38 MAP

kinase. For example, 2-bromo-3-chlorothiophene was coupled with 2-chloro-4-nitrobenzoyl chloride to give 2-chloro-4-nitrophenyl 3-chloro-2-thienyl ketone (44%), which was reduced to the amine (95%). Addition of 2-bromotoluene afforded II (31%). The latter displayed potent inhibitory activity against p38α MAP kinase with IC50 of 93.3 nM and inhibited production of IL-1β, TNF-α, and PMN-superoxide with IC50 values of 72 nM, 17 nM, and 6.3 nM, resp. Thus, I and compns. of I with other active components are useful as antiinflammatory agents in the prophylaxis or treatment of inflammatory diseases or conditions (no data).

L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

2002:591707 Document No. 137:140509 Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes. Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony (Pfizer Products Inc., USA). Eur. Pat. Appl. EP 1229034 A1 **20020807**, 180 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2002-250202 20020111. PRIORITY: US 2001-265240P 20010131.

GI



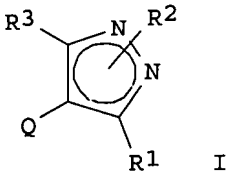
I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepared (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aqueous NaOH was added to the suspension, and the reaction mixture was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

L4 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

2000:881141 Document No. 134:29414 Preparation of substituted pyrazole compounds as p38 **MAP kinase inhibitors**.
Minami, Nobuyoshi; Sato, Michitaka; Hasumi, Koichi; Yamamoto, Norio; Keino, Katsuyuki; Matsui, Teruaki; Kanada, Arihiro; Ohta, Shuji; Saito, Takahisa; Sato, Shuichiro; Asagarasu, Akira; Doi, Satoshi; Kobayashi, Motohiro; Sato, Jun; Asano, Hajime (Teikoku Hormone Mfg. Co., Ltd., Japan). PCT Int. Appl. WO 2000075131 A1 **20001214**, 85 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP3547 20000601. PRIORITY: JP 1999-156683 19990603; JP 1999-157011 19990603.

GI



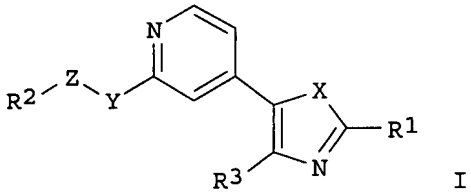
I

AB Substituted pyrazole compds. of general formula (I; wherein R1 is -CH(OH)-CH(R4)-(A)n-Y, -CH2-CH(R4)-(A)n-Y, -CO-B1-A-Y, or the like (wherein A is lower alkylene; Y is aryl which may be substituted with, e.g., halogeno, or the like; R4 is hydrogen or lower alkyl; B1 is -CH(R4)- or -N(R4)-; and n is 0 or 1); R2 is hydrogen, lower alkyl which may be substituted with hydroxyl or the like, or aralkyl; R3 is Ph which may be substituted with halogeno or the like, or pyridyl; and Q is pyridyl or quinolyl) or salts thereof are prepared These compds. exhibit an excellent p38 MAP kinase inhibiting effect and are useful in the prevention or treatment of tumor necrosis factor α-related diseases, interleukin 1-related diseases, interleukin 6-related diseases, or cyclooxygenase II-related diseases. The above diseases include chronic articular rheumatism, multiple sclerosis, osteoarthritis (arthrosis deformans), **psoriasis**, HIV, asthma, septic shock, inflammatory intestinal disease, Crohn's disease, Alzheimer's disease, diabetes, cachexia, osteoporosis, graft-vs.-host disease, adult respiratory distress syndrome, arteriosclerosis, gout, glomerulus nephritis (glomerulonephritis), ischemic heart failure, ulcerative colitis, septicemia, cerebral malaria, restenosis, nephritis, systemic lupus erythematosus, thrombosis, bone resorption disease, chronic pulmonary inflammation disease, heart or kidney reperfusion disorder, cancer, Reiter's syndrome, imminent abortion, eczema, homograft rejection, seizure, fever, Behcet's disease, neuralgia, meningitis, sunburn, contact dermatitis, acute synovitis, spondylitis, muscle degeneration, neovascularization, conjunctivitis, psoriatic arthritis, viral myocarditis, pancreatitis, hemorrhage, arthritis, endotoxin shock, parasitic infection, tuberculosis, myocardial infarction, Hansen's disease, diabetic conjunctivitis, irritable bowel syndrome, transplant rejection, burn, bronchitis, ischemic heart disease, pneumonia, remission of swelling, backache (low back pain), pharyngolaryngitis, Kawasaki disease, spinal cord disease, atopic dermatitis, etc. Thus, 3(5)-(4-fluorophenyl)-5(3)-(3-phenylpropyl)-4-(4-pyridyl)pyrazole was dissolved in DMF, treated with NaH at room temperature for 40 min, and alkylated by 2-benzyloxyethyl methanesulfonate at room temperature for 3 h, followed by hydrogenolysis over Pd(OH)2 (Pearlman catalyst) in EtOH and cyclohexane to give a mixture of 5-(4-fluorophenyl)-1-(2-hydroxyethyl)-3-(3-phenylpropyl)-4-(4-pyridyl)pyrazole and 3-(4-fluorophenyl)-1-(2-hydroxyethyl)-5-(3-phenylpropyl)-4-(4-pyridyl)pyrazole. The latter compds. and 3(5)-(4-fluorophenyl)-4-(4-pyridyl)-5(3)-[3-(3-pyridyl)propyl]pyrazole showed IC50 of 0.042 and 0.0000115 nM against p38 MAP kinase, resp.

L4 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

2000:772628 Document No. 133:321879 Preparation of 5-pyridyl-1,3-azole compounds as antagonists of adenosine A3 receptor, process for producing the same and use thereof. Ohkawa, Shigenori; Kanzaki, Naoyuki; Miwatashi, Seiji (Takeda Chemical Industries, Ltd., Japan). PCT Int. Appl. WO 2000064894 A1 **20001102**, 152 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP2575 20000420. PRIORITY: JP 1999-116686 19990423; JP 1999-224650 19990806.

GI



I

AB Optionally N-oxidized compds. represented by general formula (I) salts thereof [wherein R1 represents hydrogen, hydrocarbyl, a heterocycle, amino or acyl; R2 represents an aromatic group; R3 represents hydrogen, pyridyl or aromatic hydrocarbyl; X represents oxygen or optionally oxidized sulfur; Y represents a bond, oxygen, optionally oxidized sulfur or NR4 (wherein R4 represents hydrogen, hydrocarbyl, or acyl); and Z represents a bond or a divalent chain hydrocarbyl] are prepared These compds. are usable as preventives or remedies for diseases in association with adenosine A3 receptor because of having excellent adenosine A3 receptor antagonism thereof. Moreover, the compds. I or salts thereof exhibit excellent effects of inhibiting p38 MAP kinase and inhibiting TNF-α and, therefore, are also usable as preventives or remedies for diseases in association with p38 MAP kinase or TNF-α. Above diseases include asthma, allergies, brain edema, cerebral vascular disorders, head injuries, inflammation, Addison's disease, autoimmune hemolytic anemia, Crohn's disease, **psoriasis**, rheumatism, spinal cord injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, diabetes, arthritis, septicemia, ulcerative colitis, chronic pneumonia, silicosis, lung sarcoidosis, pulmonary tuberculosis, cachexia, arteriosclerosis, Creutzfeldt-Jakob disease, virus infection, atopic dermatitis, systemic lupus erythematosus, AIDS encephalopathy, meningitis, angina pectoris, myocardial infarction, ischemic heart failure, hepatitis, transplant, dialysis hypotension, and frequent disseminated intravascular coagulation. Thus, bromination of 2-(2-benzoylamino-4-pyridyl)-1-(4-methoxyphenyl)ethanone with Br in AcOH at room temperature for 1 h followed by cyclocondensation of the bromination product with thiourea in the presence of Et3N in MeCN at 80° for 5 h gave N-[4-[2-amino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]-2-pyridyl]benzamide (II). II showed IC50 of 0.020 μM against p38 MAP kinase and 0.014 μM for inhibiting the production of TNF-α in THP-1 cells.

L4 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

2000:688272 Document No. 133:280563 Human antibodies that bind human IL-12 and methods for producing. Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom, Angela; Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen, Sara; Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L. (Basf A.-G., Germany; Genetics Institute Inc.; et al.). PCT Int. Appl. WO 2000056772 A1 **20000928**, 377 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US7946 20000324. PRIORITY: US 1999-PV126603 19990325.

AB Human antibodies, preferably recombinant human antibodies, that

specifically bind to human interleukin-12 (hIL-12) are disclosed. Preferred antibodies have high affinity for hIL-12 and neutralize hIL-12 activity in vitro and in vivo . An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. The antibodies, or antibody portions, of the invention are useful for detecting hIL-12 and for inhibiting hIL-12 activity, e.g., in a human subject suffering from a disorder in which hIL-12 activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human antibodies of the invention, and methods of synthesizing the recombinant human antibodies, are also encompassed by the invention.

L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

2000:417390 Document No. 134:40852 TNF-α and serum induce SKALP/elafin gene expression in human keratinocytes by a p38 MAP kinase-dependent pathway. Pfundt, Rolph; Wingens, Miriam; Bergers, Mieke; Zweers, Manon; Frenken, Marco; Schalkwijk, Joost (Department of Dermatology, University Hospital Nijmegen, Nijmegen, 6500 HB, Neth.). Archives of Dermatological Research, 292(4), 180-187 (English) **2000**. CODEN: ADREDL. ISSN: 0340-3696. Publisher: Springer-Verlag.

AB Keratinocytes of inflamed epidermis (**psoriasis**, wound healing) are hyperproliferative and display an abnormal differentiation program. This regenerative differentiation pathway is characterized by the induction of genes that are not expressed by keratinocytes in normal skin, such as the cytokeratins CK6, CK16, CK17, and the proteinase inhibitor SKALP/elafin. Here, the authors investigated the induction and regulation of SKALP expression as a marker for regenerative differentiation in epidermal keratinocytes. Various cytokines and growth factors known to be present in psoriatic epidermis were examined for their ability to induce SKALP gene expression in cultured human keratinocytes. Tumor necrosis factor-α (TNF-α) and serum were potent inducers of SKALP expression at both the mRNA and the protein levels. SB202190 or SB203580, two specific p38 **MAP kinase inhibitors** almost completely blocked the induction of SKALP expression by TNF-α and serum. Thus, in keratinocytes, p38 activity is crucial for the induction of SKALP gene expression. These findings could be relevant for the elucidation of the mechanisms involved in normal and disturbed epidermal differentiation.

L4 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

1999:764037 Document No. 132:3367 Preparation of 1-piperidinyl-3-pyrimidinylimidazoles as ERK/**MAP kinase inhibitors**.. Adams, Jerry Leroy (SmithKline Beecham Corporation, USA). PCT Int. Appl. WO 9961440 A1 **19991202**, 20 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US11455 19990525. PRIORITY: US 1998-86645 19980526.

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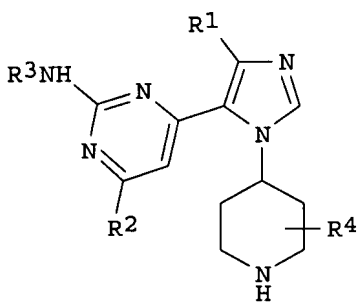

I

AB Title compds. [I; R1 = H, halo, alkyl, alkoxy, aralkyl; R2 = H,

(substituted) alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl; R3 = H, alkyl; R4 = H, (substituted) alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl], are claimed (no biol. or synthetic data).

L4 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
1999:426052 Document No. 131:67573 From FKBP12 to IMPDH. Ten years of immunology targets at Vertex. Murcko, Mark (Vertex Pharmaceuticals Inc., Cambridge, MA, USA). Chimia, 53(6), 301 (English) **1999**. CODEN: CHIMAD. ISSN: 0009-4293. Publisher: Neue Schweizerische Chemische Gesellschaft.
AB A review is given with 2 refs. 10 Yr of research are described on some different autoimmune and inflammatory targets like **psoriasis**, rheumatoid arthritis, asthma, hepatitis C, or organ-transplant rejection. The design of new inhibitors was based on FLBP12, the target for FK506. Other projects focussed on a ternary complex formed by calcineurin (FKBP12), p38 mitogen-activated protein (**MAP**) **kinase inhibitors**, the inhibitor VX-740 for interleukin-1β (IL-1β)-converting enzyme (ICE) as a treatment for rheumatoid arthritis (RA), inosine-5'-monophosphate dehydrogenase (IMPDH), and VX-497 for immunosuppressive therapy.

L4 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
1996:411062 Document No. 125:96099 2-(2-Amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran for treating proliferative disorders. Bridges, Alexander J.; Saltiel, Alan R. (Warner-Lambert Co., USA). U.S. US 5525625 A **19960611**, 7 pp. (English). CODEN: USXXAM. APPLICATION: US 1995-378131 19950124.
AB 2-(2-Amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran (I) inhibits Map kinase or Erk kinase and is effective in treating cancer and other proliferative diseases such as **psoriasis** and restenosis. I was subjected to Cascade assay for inhibitors of the Map kinase pathway. I also showed inhibition of PDGF-stimulated thymidine incorporation in Balb 3T3 and K-Balb 3T3 cells. A tablet containing 50 mg I and an oral suspension containing 500 mg I in 100 mL aqueous solution were formulated.

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L5          310 ERBB2 ANTIBOD?

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L6            2 L5 AND PSORIASIS

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L7            2 DUP REMOVE L6 (0 DUPLICATES REMOVED)

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L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-**ErbB2 antibodies**. Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized antibodies to HER2. In one example, an anti-HER2 antibody is shown to inhibit heregulin-induced activation of Akt kinase and erbB2 association with erbB3. The present application describes treatment of non-malignant indications, such as **psoriasis**, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-**ErbB2 antibodies** (e.g. rhuMAb 2C4).

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
1996:254276 Document No. 124:340904 Methods and bifunctional ligands for specific tumor inhibition by blood coagulation in tumor vasculature. Thorpe, Philip E.; Edgington, Thomas S. (Univ. of Texas System, USA; Scripps Res. Inst.). PCT Int. Appl. WO 9601653 A1 19960125, 325 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US7439 19950607. PRIORITY: US 1994-273567 19940711.

AB Bispecific binding ligands are provided which bind through a 1st binding region to a disease-related target cell, e.g. a tumor cell or tumor vasculature; the 2nd region has coagulation-promoting activity or is a binding region for a coagulation factor. Since tumor vasculature is prothrombotic and is predisposed towards coagulation, these targeted coagulants selectively induce blood coagulation in vessels supplying the tumor and cause death of tumor cells. The bispecific binding ligand may be a bispecific (monoclonal) antibody, or the 2 ligands may be connected by a (selectively cleavable) covalent bond, a chemical linking agent, an avidin-biotin linkage, etc. The target of the 1st binding region may be a cytokine-inducible component, and cytokine may be release in response to a leukocyte-activating antibody; this may be a bispecific antibody which crosslinks activated leukocytes with tumor cells. Alternatively, the target of the 1st binding region may be a component (e.g. E- or P-selectin) which is inducible by thrombin, where thrombin production is induced by administration of a bispecific antibody which binds to a tumor cell and to tissue factor, prothrombin, factor VII/VIIa, factor IX/IXa, etc. Thus, a coaguligand (bispecific antibody capable of targeting a coagulant to a tumor site) was prepared by chemical coupling an Fab' fragment from monoclonal antibody B21-2 (which reacts with I-Ad antigen expressed on A20 B-cell lymphoma cells and on the vasculature of C1300 transfectant mouse tumors) with an Fab' fragment from monoclonal antibody 10H10 (which reacts with human tissue factor). Incubation of A20 cells with this bispecific antibody and recombinant human truncated tissue factor resulted in tethering of tissue factor to the cells; plasma added to the A20 cell-tissue factor complex coagulated rapidly. Kits comprising the bifunctional ligand, a 2nd ligand, and optionally a drug for conjunctive therapy are described.

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L8 4 L5 AND MAP KINASE

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L9 4 DUP REMOVE L8 (0 DUPLICATES REMOVED)

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L9 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
2004:467984 Document No. 141:22217 Therapy of non-malignant diseases or disorders with anti-**ErbB2 antibodies**. Sliwkowski, Mark X.; Brunetta, Paul G. (Genentech, Inc., USA). PCT Int. Appl. WO

2004048525 A2 20040610, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US37367 20031121. PRIORITY: US 2002-428027P 20021121.

AB The authors disclose the preparation and biol. activity of murine and humanized antibodies to HER2. In one example, an anti-HER2 antibody is shown to inhibit heregulin-induced activation of Akt kinase and erbB2 association with erbB3. The present application describes treatment of non-malignant indications, such as psoriasis, endometriosis, scleroderma, vascular diseases or disorders, respiratory disease, colon polyps or fibroadenoma, with anti-**ErbB2 antibodies** (e.g. rhuMAb 2C4).

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN

2004:59563 Document No. 140:122766 Treatment of cancer with anti-**ErbB2 antibodies**. Kelsey, Stephen M.; Sliwkowski, Mark X. (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2004013667 A1 20040122, 56 pp., Cont.-in-part of U.S. Ser. No. 268,501. (English). CODEN: USXXCO. APPLICATION: US 2003-608626 20030627. PRIORITY: US 1999-141316P 19990625; US 2000-602812 20000623; US 2002-268501 20021010.

AB The present application describes methods for treating cancer with anti-**ErbB2 antibodies**, such as anti-**ErbB2 antibodies** that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal antibody 2C4 was effective in inhibiting breast cancer tumor growth in mice with MCF7 xenografts.

L9 ANSWER 3 OF 4 MEDLINE on STN

2004584558. PubMed ID: 15557433. Role of ErbB2 in Corneal Epithelial Wound Healing. Xu Ke-Ping; Riggs April; Ding Yu; Yu Fu-Shin X. (Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta, Georgia.) Investigative ophthalmology & visual science, (2004 Dec) Vol. 45, No. 12, pp. 4277-83. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: Human corneal epithelial cells (HCECs) were functionally depleted of erbB2 to elucidate its role in epidermal growth factor (EGF) receptor (EGFR) activation-dependent cell migration. METHODS: The retrovirus pBabe-5R, which encodes an erbB2 single-chain antibody with an endoplasmic reticulum (ER)-targeting sequence, and control pBabe-puro were used to infect THCE cells (an SV40-immortalized HCEC line). Several cell lines expressing 5R were selected along with a pBabe-puro control line. The depletion of erbB2 was verified by cell surface biotinylation of proteins, followed by streptavidin precipitation and subsequent detection of erbB2 by immunoblot analysis. Activation of erbBs was analyzed by immunoprecipitation using the phosphotyrosine antibody pY20, followed by Western blot analysis with erbB1 or **erbB2 antibodies**. Phosphorylation of extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3'-kinase (PI3K) was analyzed by Western blot with antibodies specific to phosphorylated proteins. Effects of erbB2 depletion on heparin-binding EGF-like growth factor (HB-EGF)-induced cell migration were determined by Boyden chamber migration assay and by scratch wound assay. RESULTS: Wounding induced erbB2 tyrosine phosphorylation. Expression of 5R encoding an erbB2 single-chain antibody with an endoplasmic reticulum-targeting sequence depleted the cell surface expression of erbB2 in HCECs. Wounding resulted in a rapid increase in the phosphorylation of erbB1 in both 5R-expressing and control cells, whereas wound-induced erbB2 phosphorylation in 5R-expressing cells was not detectable. Depletion of functional erbB2 attenuated the healing of scratch wounds in the presence of HB-EGF and impaired both chemotactic migration stimulated by HB-EGF and haptotactic migration toward a

fibronectin-collagen I (3:1; FNC) coating mix. Expression of 5R affected both the intensity and the duration of wound-induced, EGFR-elicited ERK and PI3K activation. Inhibition of ERK and PI3K pathways in cultured porcine corneas impaired ex vivo epithelial wound healing. CONCLUSIONS: ErbB2 serves as a critical component that couples erbB receptor tyrosine kinase to the migration machinery of corneal epithelial cells.

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN

2004:369738 Document No. 141:415821 DDS and anti-cancer monoclonal antibody therapy. Sasaki, Shigeru; Imai, Kohzoh (First Department of Internal Medicine, Sapporo Medical University, Japan). Biotherapy (Tokyo, Japan), 18(2), 175-182 (Japanese) 2004. CODEN: BITPE9. ISSN: 0914-2223. Publisher: Gan to Kagaku Ryohosha.

AB Monoclonal antibody (MoAb) is a ideal tool for drug delivery systems (DDS). Recently, therapeutic MoAbs have become a major strategy in clin. oncol. owing to their ability to bind specifically to cancer cells and induce anti-cancer effects by the cytotoxicity of MoAb itself, complement-mediated cytotoxicity, antibody-dependent cell mediated cytotoxicity, and focused delivery of radiation, anti-cancer drugs or cellular toxins by conjugated antibody. The recent clin. success of anti-cancer MoAbs has created a great step forward in DDS for cancer. The Erb-B receptor family is implicated in the malignant transformation of several tumor types and is frequently overexpressed in breast, ovarian and other tumors. We established an anti-ErbB-2 mouse-human chimeric MoAb, CH401, which was able to kill cancer cells overexpressing the ErbB-2 in vitro and in vivo. The anal. of the killing mechanism indicated that CH401 might be the first anti-ErbB-2 mouse-human chimeric MoAb that can induce the apoptosis of cancer cells. To study the biochem. mechanisms of apoptosis induced by CH401, we investigated the **MAP kinase** and Akt signaling and caspase pathways. The result was that CH401 activated first the JNK/p38 pathway and down-regulated the ERK and Akt pathway, and then caspase-3/8 pathways in ErbB-2 expressing cells. Our results indicated that CH401 treatment may prove to be very useful for cancer therapy.